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EXAMINER

SHARAREH, SHAHNAM J

ART UNIT	PAPER NUMBER
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1617

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/699,679	Applicant(s) UNGER ET AL.	
	Examiner Shahnam Sharareh	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 May 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4,6-35 and 54-63 is/are pending in the application.
- 4a) Of the above claim(s) 12 and 13 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3,6-11,14-20,25-35 and 54-63 is/are rejected.
- 7) ☒ Claim(s) 4 and 21-24 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>6/21/04, 10/22/02</u> . | 6) <input type="checkbox"/> Other: _____ |

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 13, 2004 has been entered.

Claims 1, 3-4, 6-35, 54-63 are pending.

Examination continues on the claims to the extent that they read on the elected species. Applicant has made an election of Group XII in Paper No. 22B, filed on April 10, 2003. Applicant also has made an election of accordingly the search is still directed to such species wherein R1 is acyl of 18 carbons, R2 is H, R3 is ethylene, R4 is acyl of 18 carbons, P is PEG-3400 and T is a peptide having sequence CRGDC wherein the two cytosines are linked together via a disulfide linkage. Claims 1, 3-4, 6-11, 14-35 and 54-63 are directed to said species and thus under consideration.

Because applicant had not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Accordingly, claims 1-4, 6-35, 54-63 are examined to the extent that they are read on Group XII invention. Other inventions enumerated as Groups I-XI stand thus withdrawn as being directed to the non-elected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other

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appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 12-13 are also withdrawn from further consideration because they are not directed to the elected species.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Examiner also states that Applicant's understanding is correct in that if the elected subject matter is found to be allowable over the prior art the search, the examination will be expanded to cover other species until it includes the full scope of the generic claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

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2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-4, 6-11, 14-20, 26-35 and 54-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al WO 96/40285 ("WO '285") in view of Ruosiahti et al US Patent 5,536,814 and Siegel et al US Patent 6,086,573.

The scopes of the claims are directed to compounds and targeted vesicle-containing, 3-4, 6-11, 15-16, 54, 61-63 are directed to compounds within the genus of those set forth in claim 1. Claims 17-35 and 55-60 are directed to compositions comprising the compounds.

WO '285 teaches all elements of the instant compounds within the subgenus of elected group (see claim 136-149, page 179-182; claim 164, page 183). The corresponding functional groups in the compounds of WO '285 are as follows:

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Functional Group of the Instant Compound	Instantly Elected Species	Functional Group of the Compounds of WO '285	Corresponding Subgenus	Citation
X1, X2	C=X3, C=X3-N(R8), -C=X3-N(R8)-C(=X3)-, wherein X3 is O or S	X2, X3	R5-X4-C(=X5)-, R5-C(=X5)-X4, -X4-C(=X5)-R5, R5-X4-C(=X5)-R5-C(=X5)-X4, wherein X1 is NR4 , R3 is a H, R4 is an alkyl 1-10 carbons , R5 is a direct bond, X4 is O, NR4 or S, and X5 is O or S	Page 179, lines 15-22, 25-27. Page 180, lines 1-5
R3	Alkelene	R2	Alkelene of 1 to 30 carbons	Page 180, line 1
R1, R2, R4	Acyl of 18 carbons	R1	Alkyl of 1-50 carbons	Page 179, line 27
P	Peg-3400	Z	Hydrophilic polymer, such as PEG, preferably having MW of about 2000-5000	Page 179, line 25. page 44, lines 1-6
T	CRGDC peptide	Q	Cyclic peptides	Page 179, line 26. page 183, line 13-15. pages 50, 55-58

Examiner draws Applicant's attention to WO' 285 claim 135 at page 179. Accordingly, when X1 is NR4 and R4 is alkyl of 1-10 carbons, WO '285 teaches the subgenus of compounds that encompass compounds of claim 1 and 54 of invention Group XII. Specifically, WO '285 teaches that cyclic peptides can be used as targeting agents. WO' 285 also teaches that such compounds are used to prepare targeted vesicles wherein said vesicles such as liposomes comprising a phospholipid, perfluorobutane gas, and a bioactive agent. See page 29-30; page 90, lines 15-page 91, lines 11; page 108, lines 17-page 109, lines 32 examples 18-21, 37; claims 1-30).

Examiner takes the position that the core carbon atom of the compound of page 179, lines 13-15 meets the instant diamide structure. This carbon atom is

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linked to R2-X1-R1 at one end, X1-R1 at the other, and R3 at the other position.

R2 is defined as an alkylene moiety of 1-30 carbons encompassing an ethylene.

X1 can be -NR₄ wherein R₄ is a hydrogen or alkyl. Such moiety meets the limitation of instant N-R₅. Finally, R₁ of the prior art is an alkyl of 1-50 carbons, which reads on the instant R₄, and R₂ as an acyl group having 16-23 carbons.

All other limitations are described below as the corresponding groups. (see claim 136-149, page 179-182; claim 164, page 183).

WO'285 only lacks the explicit use of CRGDC as the targeting agent, PEG-3400 as the hydrophilic polymer, and urokinase as the bioactive agent.

Ruoslahti is used to show that CRGDC is a cyclic peptide and a suitable targeting agent for recognizing fibronectin- and vitronectin-binding integrins of cell surface. Specifically, Ruoslahti teaches that CRGDC motif include the following amino acid sequences of cys-arg-gly-asp-cys (see abstract, col 2, lines 35-41; Seq ID 10, col 15) which is the same as the instant targeting agent CRGDC.

Siegel is used to merely show that combination of a thrombolytic agent such as urokinase with a gaseous ultrasound contrast agent enhance thrombolytic effects of the thrombolytic agent. (see abstract, col 6, line 65-col 8, line 20).

Accordingly it would have been obvious to one of ordinary skill in the art at the time of invention to employ compounds of WO '285 with PEG-3400, because as suggested by WO'285 patent itself the average MW of PEG of choice must be within 2000-5000. Further, it would have been obvious to substitute the RGD

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targeting agent of WO '285 patent with CRGDC of Ruoslahti, because WO '285 itself suggested the such cyclic peptides are suitable targeting agents. Thus, the ordinary skill in the art would have had a reasonable expectation of success to prepare suitable compounds as for use in preparing targeted vesicles.

Furthermore, as suggested by Siegel use of urokinase with a gaseous contrast agent shows beneficial clinical results, accordingly, using urokinase in combination with said targeted vesicles would have been obvious, because there would have been reasonable expectation of success, as explained by Siegel, to improve thrombolytic activity of urokinase.

Response to Arguments

Applicant's arguments filed May 13, 2004 have been fully considered but they are not persuasive.

Applicant argues that the newly presented claims require the compounds and compositions to contain acyl groups at position R^1 and R^4 wherein they have 16-23 carbons. Applicant then argues that such modification is not suggested in the prior art. (see pages 11-12 of the Response).

In response Examiner states that contrary to Applicants arguments the combined teachings of the prior art meet all elements of the instant rejected claims. Specifically, WO '285 teaches di-fatty acid amide compounds encompassed by those of the instantly claimed compounds. The instant R^1 and R^4 is the same as R^4 of WO '285 when X^1 is NR^4 . Thus, the primary reference clearly teaches all elements of the instantly argued di-fatty acid amide compounds having 18 carbon acyl.

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The primary reference only lacks the specific targeting agent and the specific hydrophilic polymers. Such lack of disclosure is remedied by the secondary references as reasoned above. Thus, the rejection of claims is proper.

Applicant also presents an abstract authored by present inventors demonstrating that di-fatty acid amide compounds provide better targeting and anchoring capabilities when they are incorporated into a targeting vesicle. Applicant then argues that such unexpected results are evidence of nonobviousness. (see Response at pages 12-13).

Such line of arguments is found partially persuasive. Accordingly, rejection of claims 21-24 is withdrawn. However, claims 1, 3-4, 6-11, 14-20, 27-35, 54-60 stand rejected.

In response to applicant's arguments, Examiner states objective evidence of nonobviousness must commensurate in scope with the claims. See MPEP § 716. Here, the provided abstract, even though relevant, is not commensurate with the scope of the rejected claims.

The presented abstract titled *Synthesis, Characterization, and Calorimetric Studies of a Series of Novel Bioconjugates for the Selective Targeting of Microbubbles of GPIIb/IIIa Receptors on Vascular Thrombi* by Patricia Schumann et al, is directed to the use of diaminobutyl-PEG-GGGRGDS conjugated with dipalmitoylphosphatidylcholine in a liposomal formulation. Accordingly, the authors concluded that 18 and 16 carbon chains inserted into a bilayer targeted liposome provide better anchoring characteristics for liposome. (see figures 3-4 and conclusion of the abstract).

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The data provided in said abstract is directed to the use of di-fatty acid amide having 16-18 carbon chains in a liposome comprising a phosphatidylcholine moiety. Said data is not directed to all types of vesicles compositions or compounds encompassed by the rejected claims. In fact, the data elaborated in the abstract neither provide any unexpected result for preparing instant compounds over those di-fatty acid amides of WO '285, nor does it provide any unexpected results for lipid containing vesicles described in WO '285 comprising a perfluorocarbon gas.

Examiner views the novelty of the compounds of claim 1 to revolve around the fact that whether the compound itself is described by the teachings of the prior cited art. Not whether a use of such compound can provide unexpected results. WO '285 teaches the instant compounds except the specific polymeric and targeting moieties. The secondary references remedy such teachings. Therefore, the rejection is proper.

Claim Objections

Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 4 is directed to R1 and R4 having 15 carbons. However the instant parent claim 1 requires such groups to at least have 16 carbons.

Claim 4 is also depended on the canceled claim 2. Appropriate correction is requested.

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Claims 21-24 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed.

This is a continuation of applicant's earlier Application No. 09/699,679. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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